UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/651,290	08/30/2000	Marcin S. Filutowicz	P00154US/13238/00016	2591

27114 7590 03/19/2004

QUARLES & BRADY LLP
411 E. WISCONSIN AVENUE, SUITE 2040
MILWAUKEE, WI 53202-4497

EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/651,290	FILUTOWICZ, MARCIN S.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 16-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 16-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This Office Action is responsive to Applicant's amendment and response filed November 24, 2003. Claims 11-12, 16-27 have been amended. Claims 13-15 and 28-30 have been cancelled. Applicants Declaration filed under 37 C.F.R. 1.132 and Exhibits A-G filed November 24, 2004 are acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

3. In view of Applicant's amendment and response, the rejection of claim 12 under 35 U.S.C. 112, second paragraph is withdrawn.

Rejections Maintained

4. The rejection of claims 1-12 and 16-27 under 35 U.S.C. 112, first paragraph is maintained for the reasons set forth on pages 2-3 of the previous Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.*

The claims are drawn to a recombinant bacterium which comprises a non-pathogenic bacterial cell harboring at least one transmissible plasmid comprising: an origin of replication wherein the initiation of replication at the origin is negatively controlled by a plasmid replication repressor, an origin of transfer and at least one screenable marker gene. The amended claims contain new matter. Applicant has amended the claimed invention from an antibacterial agent to a recombinant bacterium. Applicant has not set forth where in the instant specification that support can be found for the amended claims.

Applicant urges that the term "recombinant bacterium" is disclosed in the instant specification. Applicant urges that Example 2 of the specification discloses the use of a recombinant bacterium".

Applicant's arguments filed November 24, 2003 have been fully considered but they are not persuasive. Although the specification teaches the use of recombinant bacteria, the specification has not shown that the recombinant bacteria comprising plasmids have antibacterial properties. Nowhere in the instant disclosure has the specification defined the "recombinant bacterium" as "antibacterial agents". The experimental examples merely show that recombinant bacteria can be transformed with plasmids. Therefore, the new matter rejection is maintained.

5. The rejection of claims 1-12 and 16-27 under 35 U.S.C. 112, first paragraph is maintained for the reasons set forth on pages 4- 9 of the previous Office Action.

The rejection was on the grounds that the specification contained subject matter which was not described in the in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to an antibacterial agent which comprises a non-pathogenic bacterial cell harboring at least one transmissible plasmid comprising: an origin of replication wherein the initiation of replication at the origin is negatively controlled by a plasmid replication repressor, an origin of transfer and optionally, at least one screenable marker gene and a pharmaceutical preparation comprising the antibacterial agent.

The specification generically claims an antibacterial agent that comprises a non-pathogenic donor bacterial cell harboring at least one transmissible plasmid comprising an origin of replication, an origin of transfer and optionally at least one screenable gene marker. The claimed invention further includes a plurality of microorganisms of which the donor cell or recipient cell can be obtained. The specification does not provide substantive evidence that the claimed antibacterial agent can maintain stability or that the pharmaceutical preparation comprising the antibacterial agent is capable of treating

bacterial infections. This demonstration is required for the skilled artisan to be able to use the claimed invention for the intended purpose of treating bacterial infections. Without this demonstration, the skilled artisan would not be able to reasonably predict whether the claimed invention could survive *in vivo* use or whether the artisan would be able to predict if the administration of the claimed pharmaceutical preparation, would be able to treat bacterial infections.

There are several factors that contribute to the stability of plasmids that are well known in the art. These factors include: 1) the ability of conjugative transfer within and between genera, 2) essential components required to ensure stabilization 3) mating pair stabilization and 4) compatibility between the donor and recipient cell. The ability to reasonably predict the capacity of plasmids to be conjugatively transferred within genera and especially between genera, maintain stability is problematic. This is evidenced by Ambrozic et al, *Microbiology (ENGLAND), February 1998, 144(Pt 2), p. 343-352).* Ambrozic et al teach that conjugal transfer was demonstrated with low frequency to *Klebsiella pneumoniae* suggesting that a natural barrier effectively bars transfer. Specific sequences are also required for the complete stabilization of plasmids. For example, Roberts et al, *(Journal of Bacteriology, November 1990, 172 (11), p. 6204-6216)* teach that one of the regions responsible for stable inheritance of the broad host range plasmid RK2 is contained within the PstI C fragments. Robert et al teach that the PSTI C fragment itself is not required for stabilization activity, however the PSTI C fragment encodes a multimer resolution system which required adjacent sequence to maintain complete stabilization. Mating stabilization during conjugative transfer between the donor and recipient cell is also required. Klimke et al, *(Journal of Bacteriology, August 1998, 180 (16), p. 4036-4043)* teach that mating stabilization occurs during conjugative transfer whereby the donor cell and recipient cells form a tight junction which requires pili as well as TraN and TraG (proteins involved in matting pair stabilization) in the donor cell. Klimke et al teach that the TraN and not the F pili appears to interact with OmpA and LPS moieties during conjugation, resulting in mating stabilization. Klimke et al further teach that this is the first step in efficient mobilization of DNA. Compatibility between the donor cell and the recipient cell is also necessary. This is further evidenced by Rahal et al, *(Annales de microbiologie (FRANCE), May-June 1978, 129 (4), p. 409-414).* Rahal et al teach that very few multi-resistant strains of *Vibrio cholerae* have been isolated this may be due to a high frequency of plasmids being lost due to the incompatibility of groups. Since genetic mutations are used to determine the structural and functional properties of the claimed antibacterial agent and pharmaceutical composition the predictability of which changes or mutations can be tolerated in the host and still retain similar activity requires a knowledge of and guidance with regard to which mutations can be made in the plasmid wherein stability will be maintained. The cited references have shown that unpredictability exists regarding plasmid stability. Therefore, it can be concluded that undue experimentation would be required to make and use the claimed antibacterial agent without proper guidance.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the pharmaceutical preparation commensurate in scope with these claims. The specification fails to teach

how to make and use the claimed pharmaceutical preparation. The term "pharmaceutical" encompasses the ability of the specific antigen to induce protective immunity to a host. The specification does not disclose how to formulate the pharmaceutical preparation or what dosages are required to treat a patient with a bacterial infection? The specification further does not disclose whether the antibacterial agent can be survive the mouth, stomach or intestines without being degraded or if the antibacterial agent is capable of reach the target organs necessary to treat a particular bacterial infection. Therefore, it is unclear as to how to formulate a pharmaceutical preparation comprising the antibacterial agent which will treat **any** bacterial infection.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting a stable antibacterial agent and pharmaceutical preparation that would achieve a desire level of success when administered to a patient with a bacterial infection that is capable of treating that bacterial infection, 3) there are limited working examples which suggest the desired results of a antibacterial agent that is to be used in a pharmaceutical preparation to treat any bacterial infection, 4) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention.

Applicant urges that the specification only needs to be enabled for one use and the enablement for *in vivo* pharmaceutical use is not necessary, if another use is enabled. Applicant urges that the specification teaches that the invention can be used on meat, other food, including animal feed to eliminate bacteria. Applicant asserts that their invention is enabled for eliminating bacteria in animal feed. Applicant urges that no undue experimentation is required to practice the claimed invention.

Applicant's arguments filed November 24, 2003 have been fully considered but they are not persuasive. The claims are broadly drawn to a recombinant bacterium which is a non-pathogenic conjugative donor bacterium habouring at least one transmissible plasmid comprising: an origin of replication wherein the initiation of replication at the origin is negatively controlled by a plasmid replication repressor, an origin of transfer and at least one screenable marker gene and a pharmaceutical preparation comprising the antibacterial agent. It should be noted that Applicant uses *Escherichia coli* as a donor bacterium in the claimed invention. It is well known in the art that *Escherichia coli* is a pathogenic microorganism.

Applicant asserts that it is well known in the art to use the claimed invention to eliminate bacteria from animal feed. It is not well known in the art to use bacteria (pathogenic bacteria) to eliminate bacteria in animal feed.

The Filutowicz Declaration under 37 C.F.R. 1.132 is submitted by the Applicant to show that the claimed invention is enabled. However, the experiments described in the Filutowicz Declaration uses plasmids and strains of bacteria that have not been disclosed or described in the specification. The Filutowicz Declaration merely shows that plasmids can be introduced into bacteria (i.e. *E. coli* strain S17-1). It must be remembered that Applicant must enable the claimed invention at the time of filing. See In re Wright (CA FC) 27 USPQ2d 1510. The statue under 35 U.S.C. 112, first paragraph requires that Applicant show how to make and use the claimed invention. Applicant has not met the burden of disclosing how to make and use the claimed invention by what is described in the instant specification. The skilled artisan would

require undue experimentation to make and use the claimed invention commensurate with the claims. Therefore, the instant specification does is not enable the claimed invention.

New Ground of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-12 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites "non-pathogenic conjugative donor bacterium". It is unclear as to what the applicant is referring? Correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 3-5 and 7-12 are rejected under 35 U.S.C. 102(b) as anticipated by Metcalf et al *(Plasmid, 1996 Jan;35(1):1-13).*

The claims are drawn to a recombinant bacterium which comprises a non-pathogenic bacterial cell harboring at least one transmissible plasmid comprising: an origin of replication wherein the initiation of replication at the origin is negatively controlled by a plasmid replication repressor, an origin of transfer and at least one screenable marker gene.

Metcalf et al teach recombinant bacteria that contain plasmids that have the R6Kγ DNA replication origin (oriR $_{R6K\gamma}$) so they replicate only in bacteria supplying the Π replication protein (encoded by pir) and they can be maintained at low or high plasmid copy number (see the Abstract). Metcalf teach that the recombinant bacteria carry the RP4 transfer origin (oriT $_{RP4}$) so that they can be transferred by conjugation to a broad range of bacteria (see the Abstract). Metcalf et al teach recombinant bacteria that comprise plasmids that have at least one counter-selectable marker (see the Abstract). The claim limitation "wherein at least one recipient cell is a pathogenic bacterium does not produce the plasmid replication repressor, thereby enabling the transmissible plasmid to undergo runway replication in the recipient cell" is a limitation directed to the recipient cell and would be inherent in the prior art depending on the characteristics of the recipient cell since the plasmids as taught by Metcalf et al can be transferred by conjugation to a broad range of bacteria.

Since the Office does not have the facilities for examining and comparing applicant's recombinant bacterium with the recombinant bacterium of the prior art, the

burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the recombinant bacterium of the prior art does not possess the same material structural and functional characteristics of the claimed recombinant bacterium). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

8. Claims 1, 3-5, 7, 9, 11, 16, 18-19 , 24 and 26 are rejected under 35 U.S.C. 102(b) as anticipated by Kaniga et al *(Gene 109, 1991, 137-141).*

The claims are drawn to a recombinant bacterium which comprises a non-pathogenic bacterial cell harboring at least one transmissible plasmid comprising: an origin of replication, an origin of transfer, at least one killer gene, that upon expression in a bacterial cell, produces a product that kills the cell and at least one screenable marker gene.

Kaniga et al teach recombinant bacteria that comprise an origin of replication (*oriR6K*), the *strAB* genes encoding the streptomycin phosphotransferase (Sm^R), and origin of transfer (mobRK2), the *sacB* gene mediating sucrose sensitivity and multiple cloning sites (see the Summary). Kaniga et al teach that any gram-negative bacteria species where the expression of sacB gene in the presence of sucrose is lethal (page 141).

Since the Office does not have the facilities for examining and comparing applicant's recombinant bacterium with the recombinant bacterium of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed

product and the product of the prior art (i.e., that the recombinant bacterium of the prior art does not possess the same material structural and functional characteristics of the claimed recombinant bacterium). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-12 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 9 and 12 in particular recite "derived from". It is unclear as to what the applicant is referring? Correction is required.

10. Claims 16-27 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 24 and 27 in particular recite "derived from". It is unclear as to what the applicant is referring? Correction is required.

11. Claims 16-27 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 20 in particular recites "obtained from". It is unclear as to what the applicant is referring? Correction is required.

Status of Claims

12. No claims allowed.

13. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272–0864.

Vanessa L. Ford
Biotechnology Patent Examiner
March 16, 2004

MARK NAVARRO
PRIMARY EXAMINER